REMARKS

Claims 1, 10 and 64-67 were pending and under examination in the subject application. By the amendment, Claims 66 and 67 have been canceled without prejudice or disclaimer, and Claims 1 and 64 have been amended to incorporate the features of Claims 66 and 67. Applicant maintains that the claim amendments do not raise an issue of new matter. Support for the amendments to Claims 1 and 64 can be found at least in Claim 66 and 67 and in the previous version of the claim. Entry of the amendments is respectfully requested.

Provisional Obviousness-type Double Patenting Rejection

Applicant acknowledges the provisional rejection of Claims 1 and 10 over Claims 82-84 and 100-101 of later-filed co-pending U.S. Patent Application 10/580,962. Applicant notes that Claim 1 has herein above been amended to incorporate the features of Claim 66, which was not subject to this provisional rejection.

Rejections under 35 U.S.C. §112 First Paragraph

Claims 1, 10, 64 and 65 are rejected as failing to comply with the written description requirement of 35 U.S.C. §112, first paragraph.

Independent Claims 1 and Claim 64 have been amended to incorporate the features of Claims 66 and 67, which were not rejected, thereby obviating this rejection.

Rejections under 35 U.S.C. §103(a)

Claims 1, 10 and 64-67 are rejected as being unpatentable over Dipiperon (manufacture sheet) in view of Sanchez (US2002/0086899) and further in view of Broekkamp (U.S. Patent No. 6,150,353).

Applicant respectfully traverses this rejection.

In essence, the Examiner reiterates that the combination of pipamperone and citalopram as well as the dose of pipamperone are obvious in view of previously cited prior art, and now cites Broekkamp in support of his arguments regarding the dose of pipamperone.

Applicant respectfully maintains that the Examiner has misrepresented the cited prior art. In this respect, applicant maintains that Broekkamp is totally irrelevant as a prior art document because it teaches the opposite of the present invention and does not relate to the same disorders (see below). As such, there is no motivation to combine Broekkamp with either Dipiperon or Sanchez (see further below), and if such combination were to be made, it would not lead to the present invention (see further below). As Broekkamp cannot be combined with other prior art documents to come to the present invention, applicant believes that the Examiner's arguments in respect of the dose of pipamperone are not tenable (see further below).

Combination of pipamperone and SSRI/citalopram

Applicant respectfully maintains that the position by the Examiner represents an over-simplification of drug prescriptions. Interactions can be absent, can be negative or can be positive. Combinations of medicines are warned against and met very cautiously, as evidenced by all manufacturers' leaflets known to applicant, especially if possible interactions are not known or cannot be predicted. In this regard, in the manufacturer's leaflet, citalopram is indicated as an antidepressant, but not for treating anxiety. Also indicated is that a common side effect of citalopram is "anxiety" (see attached manufacturer's leaflet). Celexa® (Citalopram) is approved by the FDA but only to treat depression, not anxiety.

Dose of pipamperone ~ Broekkamp

In respect to the claimed daily dose of 5 to 15 mg of pipamperone, an additional prior art document (Broekkamp) was cited.

Applicant respectfully maintains that Broekkamp is mis-interpreted by the Examiner and/or that the Examiner's arguments are flawed for at least the following reasons:

(1) Broekkamp relates to the treatment of ***psychosis***;

(2) Broekkamp relates to the combination of ***one specific antidepressant, mirtazapine***, with an antipsychotic agent;

(3) Mirtazapine is ***not an SSRI***;

(4) Mirtazapine ***enhances the antipsychotic effect*** of the antipsychotic agent; and

(5) The dose of ***only*** the antipsychotic agent can be lowered as a result of such enhanced effect.

No motivation to combine Broekkamp with Dipiperon and Sanchez

First of all, Broekkamp relates exclusively to the treatment of ***psychosis***. Psychosis is not an anxiety disorder. There is no teaching in Broekkamp whatsoever that the findings therein can be extrapolated to anxiety disorders.

Broekkamp teaches compositions containing ***invariably*** the antidepressant ***mirtazapine***. Broekkamp identified the unexpected effect of mirtazapine on antipsychotic agents in psychosis. There is no teaching in Broekkamp whatsoever that the findings therein can be extrapolated from mirtazapine to any other antidepressant, even less to an SSRI. Mirtazapine is a noradrenergic and specific serotonergic antidepressant but ***not*** an SSRI. Broekkamp does not teach the combination of an SSRI antidepressant with an antipsychotic agent (cf. page 6 of the present Office Action).

As indicated above, it is implausible and an over-simplification to combine two different drugs, absent any understanding of possible interactions, although these drugs may be indicated for the same disorder. It is also implausible and an over-simplification that any dosage and the effect thereof in one disorder can be extrapolated to any other disorder.

The combination of teachings does not result in the present invention

If Dipiperon and Sanchez were to be combined to make a composition comprising pipamperone and citalopram, then Broekkamp would ***not*** provide the necessary teaching to come to the present invention (*i.e.* to lower the dose of pipamperone).

Broekkamp teaches that administration of an antipsychotic agent in combination with mirtazapine allows a lower dosing of the antipsychotic agent to achieve the same antipsychotic effect (see Column 2, lines 36-38 of Broekkamp).

In relation to the present invention, Broekkamp presents two prejudices:

(1) either Broekkamp would teach a person skilled in the art to investigate whether another antidepressant, such as a SSRI (citalopram) would augment the effect of pipamperone in the treatment of ***psychosis***,

(2) or Broekkamp would teach a person skilled in the art to investigate whether mirtazapine would augment the effect of pipamperone in the treatment of ***anxiety***.

The teaching by Broekkamp (antidepressant augmenting antipsychotic agent) is completely opposite to the present invention (pipamperone augmenting anti-anxiolytic agent).

Dose of pipamperone is not obvious in view of the prior art

(i) *The position of the Examiner is not tenable*

The Examiner cites Broekkamp in addition to Dipiperon and Sanchez to support his arguments regarding the low dose of pipamperone. In particular, the specific effect of the combination of mirtazapine and an antipsychotic agent is that mirtazapine enhances the effect of the latter, *i.e.* mirtazapine potentiates the antipsychotic agent. Only due to such an unexpected effect of mirtazapine, the concentration of the antipsychotic agent can be lowered. Broekkamp identified the unexpected effect of mirtazapine on antipsychotic agents in psychosis.

This contrasts with the arguments of the Examiner in the previous Office Action, wherein the Examiner merely stated that dose optimization is routine experimentation and as such cannot be considered inventive. Applicant therefore believes that applicant's arguments regarding the unprecedented low dose of pipamperone should be persuasive, absent a relevant teaching in Broekkamp (see above).

(ii) *Teaching in the prior art*

Dipiperon states that an ***initial dose of 40 to 80 mg*** per day should be administered for 1 to 2 weeks. The optimal anti-psychotic dose is reached after 3 to 6 weeks up to a maximum of 360 mg. It is further stated that it is recommended to ***increase the dose*** by 20 up to 120 mg per day. As such, Dipiperon teaches the skilled person to start with a low dose (which is still almost 3 to 8 times higher than the dosage in the present application), which is subsequently increased to an optimal, high dose. This is common practice to determine the optimal dosage for medicines, i.e. start low and build up, to ensure the lowest effective dose possible.

As such, Dipiperon teaches the skilled person that the starting dose should be 40 mg per day. The person skilled in the art (also knowing that determining an optimal dose

involves starting with a low, safe, and most of all non-optimal, even ineffective dose which is increased over time) would therefore have no incentive to even further lower the dose below the minimal prescribed starting dose.

(iii) *The effect of pipamperone*

It is well-known that pipamperone at the ubiquitously used high prior art doses gives rise to a neuroleptic-sedative effect (see also Ansoms et al. 1977, of record). This is the effect sought after and acknowledged in the prior art, such as "Dipiperon". There is no teaching or suggestion in the cited references to administer pipamperone at a lower dose than the recommended dose.

High dose pipamperone results in ***D2 receptor-related dopaminergic*** and ***H1 receptor-related histaminergic antagonism***, which is responsible for the neuroleptic-sedative effect. This antagonizing effect (resulting in this neuroleptic-sedative effect) is absent at the claimed low dose of 5-15 mg/day.

Citalopram is a potent and selective inhibitor of neuronal serotonin reuptake and has only very weak effects on norepinephrine and dopamine neuronal reuptake. Citalopram has ***no significant affinity*** for adrenergic (alpha1, alpha2, beta), cholinergic, GABA, ***dopaminergic***, ***histaminergic***, serotonergic ($5HT_{1A}$, $5HT_{1B}$, $5HT_2$), or benzodiazepine receptors; antagonism of such receptors has been hypothesized to be associated with various anticholinergic, sedative, and cardiovascular effects for other psychotropic drugs. In particular, the anti-obsessive-compulsive action of Citalopram is presumed to be linked to its inhibition of neuronal uptake of serotonin in the central nervous system. Citalopram blocks the reuptake of serotonin at the serotonin reuptake pump of the neuronal membrane, enhancing the actions of serotonin on $5HT_{1A}$ autoreceptors. SSRIs bind with significantly less affinity to histamine, acetylcholine, and norepinephrine receptors than tricyclic antidepressant drugs.

Thus in view of the entirely different working mechanisms of pipamperone and citalopram, it was not conceivable how citalopram would augment the neuroleptic-sedative effect of pipamperone.

(iv) *Undue burden*

In the present case the effect is dependent upon the interplay between two compounds, *i.e.* pipamperone and a SSRI. It is hindsight to combine pipamperone with a SSRI, to decrease the dose of only one compound but not the other, and to choose to lower the dose of pipamperone but not the dose of the second compound. Moreover, decreasing the dosage of one compound provokes an effect on the other compound. Considering the multitude of possible combinations, reaching the result of the present invention, *i.e.* pipamperone at 5-15 mg per day, represents an undue burden. Only by understanding the invention, *i.e.* understanding the *modus operandi*, pipamperone could be singled out, but not any other compound, at this low dosage.

Unexpected effect ~ faster onset

The Examiner asserts that a combination therapy is apparent "due to expectation of synergistic effects and therapeutic benefits" (page 7 of the present Office Action).

First, applicant respectfully points out that this assertion is not substantiated by any proof, is at most a mere wish, and is wholly imprudent regarding patients' well being absent any knowledge on interactions. Hence, a person skilled in the art would only combine two drugs, if at all, with great prudence and being well aware of side effects.

Second, the effects of the present combination are completely unexpected (see also above). In particular, even if it would be acknowledged that the skilled artisan would combine (which is denied) pipamperone (at the claimed low dose) and citalopram, then certainly the effect of pipamperone on augmenting the efficacy of citalopram and the

effect of pipamperone on a faster onset of citalopram are unexpected (a result which is substantiated by Figures 12-15 of copending U.S. Patent Applications Nos. 10/984,683 [US 2005/0203130] and 10/580,962 [US 2007/0078162]). The prior art teaches the opposite (see, e.g. Broekkamp).

Accordingly, reconsideration and withdrawal of this rejection are respectfully requested.

Supplemental Information Disclosure Statement

This Supplemental Information Disclosure Statement (SIDS) is being filed to supplement the Information Disclosure Statements filed on November 12, 2008, February 11, 2008, August 23, 2007, April 11, 2007 and August 9, 2005 in connection with the subject application.

In accordance with the duty of disclosure under 37 C.F.R. §1.56, applicant would like to direct the Examiner's attention to the references that are listed on the attached forms PTO/SB/08A-B. A copy of each non-U.S. patent documents is also attached.

Status of Corresponding European Patent

Applicant would like to direct the Examiner's attention to applicant's European patent attached hereto (EP 1 541 197 B1). The patent issued with broad claims including uses of pipamperone and a SSRI for treating an anxiety disorder.

Status of U.S. Patent Family Members

Applicant would also like to advise the Examiner of the status of co-pending patent family members.

1. U.S. Patent Application No. 10/725,965. The claims have been subject to a restriction requirement. Office Actions on the merits of the application issued on January

23, 2008 and September 15, 2008.

2. U.S. Patent Application No. 10/803,793. The claims have been subject to a restriction requirement. Office Actions on the merits of the application issued on May 3, 2007, October 19, 2007, September 2, 2008 and February 20, 2009.

3. U.S. Patent Application No. 10/984,683. The claims have been subject to a restriction requirement. Office Actions on the merits of the application issued on August 10, 2007, February 22, 2008, and October 21, 2008.

4. U.S. Patent Application No. 10/580,962. The claims have been subject to a restriction requirement (issued on March 6, 2009).

CONCLUSIONS

In view of the amendments and remarks made herein, reconsideration and withdrawal of the rejections in the February 19, 2009 Office Action are respectfully requested. If there are any minor matters preventing the allowance of the subject application, the Examiner is requested to telephone the undersigned attorney.

A check for $405.00 is enclosed for the fee for filing a Request for Continued Examination (RCE) for a small entity. No additional fee is deemed necessary in connection with the submission of this reply. However, if any other fee is required with this reply or to maintain the pendency of the subject application, authorization is hereby given to withdraw the amount of any such fee from Deposit Account No. 01-1785. Overpayments may also be credited to Deposit Account No. 01-1785.

Respectfully submitted,

AMSTER, ROTHSTEIN & EBENSTEIN LLP
Attorneys for Applicant
90 Park Avenue
New York, New York 10016
(212) 336-8000

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New York, New York

By _____
Alan D. Miller, Reg. No. 42,889